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## Final Report to US Army 7th International Conference on Hypertonic Resuscitation

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The 7th International Conference on Hypertonic Resuscitation was held at the Rebonças Convention Center, São Paulo. The meeting attendance averaged 60-100 people for eight themed sessions with 28 presentations. Each session ended with a panel discussion. There were 11 presentations on 13 November and 17 presentations on 14 November, 1996. There were 34 abstracts published in Shock which mostly were presented as poster communications.

Attached is a copy of the amended program to reflect last minute changes and published abstracts. Enclosed is a special supplement volume of Shock which contains the abstracts and acknowledges financial support. The entire program was videotaped by a commercial company in Brazil. George Kramer purchased a copy and can loan out his copy of the program (Phone: (409) 772-1906/Fax: (409) 772-8895). Original copies can still be purchased from Brazil.

### **Highlights of the meeting include:**

#### **Basic Science Animal Studies:**

1) Rat studies and studies on isolated lymphocytes and neutrophils show that hyperosmolality induced by hypertonic saline infusion can upregulate immune function with a resultant decrease in effective bacterial translocation and a lower mortality in models of shock, trauma and sepsis (David Hoyt et al., UC San Diego). (See related abstracts S24, S31, manuscripts published 96-97)

2) Studies in rats, performed at Temple University, showed improved CNS function after spinal cord compression injury if treated with 5 ml/kg of 7.5% NaCl compared to a control group (Ron Tuma et al., Jefferson Medical Center, Philadelphia). Also, hypertonic saline was shown to reduce infarct size after occlusion and reperfusion of brain vessels (Oliver Kemski et al.). Such studies support a wider use of hypertonic saline for CNS injuries. (See abstracts S24 and S25)

3) Studies in pig and dog with ischemic heart injury suggest that hypertonic saline offers little benefit (Welte et al., Munich) in treatment of heart failure. Hypertonic saline may cause a coronary blood flow steal phenomenon (Nguyen Kien et al., UC Davis) (See related abstract S16).

4) A symposium on the development of synthetic hemoglobin containing oxygen solutions had presentations on behalf of Baxter (Burhop), the U.S. Navy (Rollwagner) and university researchers (Rabinovici, Kramer, Poli de Figueiredo) testing hypertonic hemoglobin solutions. Such solutions may be the next generation of hypertonic formulations (See abstracts S01, S02, S06, S26, S27, S28).

#### **Military Use:**

5) There were presentations by representatives of the US Navy and US Army (Bruttig, Dubick and Rollwagner) on Department of Defense programs and development of small volume solutions for combat casualty care (See abstracts S26, S32, S33).

#### **Clinical Studies and Human Trials:**

6) Operating room studies were presented that tested HSD and HS-hetastarch in Jehovah's Witness patients, patients with aortic aneurysm and cardiac surgery (Max Regaller, Frank Christ and Sergio Olivera). Reported benefits were less overall volume and transfusion requirements. Several other reports of OR use, ICU use, volunteer studies were presented showing safety and suggesting efficacy—better tissue O<sub>2</sub> and improved hemodynamics (See related abstract S14, S15, S17, S18, S19, S20, S21).



7) Hypertonic saline hetastarch has received regulatory approval in Austria (Wolfgang Kroll) Brazil and Argentina and was used in the Yugoslavia conflict. Unfortunately, no significant data has been presented or made available on the use, efficacy or safety of such solutions. (See related abstract S20 and S34)

#### **Trauma Trials:**

8) The presentation of *a priori* designed cohort meta-analysis (James Holcroft et al.) using the individual patient data from 1035 patients taken from six double-blinded trials in which 250 ml of 7.5% NaCl/6% dextran 70 (HSD) were used as the initial treatment of traumatic hypotension. Mortality was reduced about 5% in patients treated with 250 ml of HSD as initial treatment and by 10% in those patients who had head injuries. (No abstract; manuscripts by Wade et al., in press 1997).

9) Of particular interest to the military was the analysis of the HSD trauma trials which focused on patients presumed to have dehydration, the upper 10% of patients with the highest serum Na levels in both the HSD group and the isotonic group. Lower survival rates occurred in both compared to normally hydrated patients, suggesting that dehydration increases the mortality of trauma. However, HSD effectively improved survival in dehydrated trauma patients, 69% vs. 39% in this matched group of patients likely to have had dehydration before trauma. HSD also improved survival in patients with penetrating injury who subsequently went to surgery. (See abstract S22)

Supplement to SHOCK Vol. 6, 1996

# SHOCK®

*Molecular, Cellular, and Systemic  
Pathobiological Aspects  
and Therapeutic Approaches*

CHOQUE 96: Second Brazilian Shock Congress  
SALT 7: Seventh International Conference  
on Hypertonic Resuscitation  
November 11-14, 1996

*The Official Journal of*

The Shock Society  
The European Shock Society  
The Brazilian Shock Society  
The International Federation of Shock Societies, and  
The Official and International Journal of the Japan Shock Society

**CHOQUE 96: Segundo Congresso Brasileiro de Choque**

**SALT 7: Sétima Conferência Internacional de Ressuscitação Hipertônica**

**São Paulo, Brasil**

**Segunda feira, 11 a Quinta feira, 14 de Novembro de 1996**

**Centro de Convenções Rebouças, São Paulo, Brasil**



**CHOQUE 96: Second Brazilian Shock Congress**

**SALT 7: Seventh International Conference on Hypertonic Resuscitation**

**São Paulo, Brazil**

**Monday, November 11 through Thursday November 14, 1996**

**Congress-site: Rebouças Convention Center, São Paulo, Brazil**

**Comitês Organizadores**

**Organizing Committees**

**CHOQUE 96**

Mauricio Rocha e Silva (Chair)

Dario Birolini

Leonardo Emílio da Silva

Renato Terzi

Samir Rasslan

**SALT 7**

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*Program amended to indicate actual chairs/presentors*

## SALT 7

### SEVENTH INTERNATIONAL SYMPOSIUM ON HYPERTONIC RESUSCITATION

November, 13, 1996

07:30 - 16:00 REGISTRATION

08:00 - 10:00 SYMPOSIUM: IMMUNOLOGICAL EFFECTS OF HYPERTONIC SOLUTIONS

Chair: David Hoyt, Univ. California, San Diego, CA, USA.

~~Roger Härtl, Univ. Berlin, Berlin, Germany.~~

THE EFFECTS OF INCREASED SODIUM ON T-CELL SIGNALING In Vitro AND In Vivid.

David Hoyt, Univ. California, San Diego, CA, USA.

EFFECTS OF HYPERTONIC SALINE RESUSCITATION ON IMMUNOSUPPRESSION FOLLOWING HEMORRHAGIC SHOCK AND SEPSIS.

Raul Coimbra, FCM Santa Casa, São Paulo, Brazil.

HYPERTONIC SALINE/DEXTRAN ATTENUATES EARLY ACTIVATION OF LEUKOCYTES AFTER TRAUMATIC BRAIN INJURY

~~Roger Härtl, Univ. Berlin, Berlin, Germany.~~

*Karl Anjors Experimental Medicine; Princeton, NJ*

10:00 - 10:15 COFFEE-BREAK

10:15 - 12:15 SYMPOSIUM: OPERATING ROOM USE OF HYPERTONIC SOLUTIONS

Chair: Ulf Haglund, Univ. Uppsala, Uppsala, Sweden.

Sérgio de Almeida Oliveira, Fac. Medicina Univ. São Paulo, São Paulo, Brazil.

HYPERTONIC SODIUM DEXTRAN IN THE MANAGEMENT OF JEHOVAH'S WITNESS PATIENTS DURING CARDIAC SURGERY

Sérgio de Almeida Oliveira, Fac. Medicina Univ. São Paulo, São Paulo, Brazil.

BENEFITS OF HYPER OSMOTIC-HYPERONCOTIC SOLUTIONS DURING ELECTIVE ABDOMINAL AORTIC ANEURYSM REPAIR.

Frank Christ, Klinikum Grosshadern, Munich, Germany.

HEMODYNAMIC AND ENDOCRINOLOGIC PARAMETERS UNDER HYPERTONIC FLUID LOADING IN PATIENTS UNDERGOING AORTIC SURGERY.

M. Ragaller, Univ. Dresden, Germany.

12:15 - 14:00 POSTERS / LUNCH

14:00 - 16:00 SYMPOSIUM: HEAD AND SPINAL TRAUMA

Chair: ~~Randall M. Chesnut, San Francisco, CA, USA.~~

*Rosalee Silva Univ of Sao Paulo*  
Dario Birolini, Fac. Medicina. Univ. São Paulo, São Paulo, Brazil.

PREHOSPITAL FLUID MANAGEMENT IN PATIENTS WITH HEAD TRAUMA.

Wolfgang Kröll, Univ. Graz, Graz, Austria

EFFECT OF HYPERTONIC SOLUTIONS ON THE CEREBRAL MICROCIRCULATION.

Oliver Kempfski, Univ. Mainz, Mainz, Germany.

HYPERTONIC SALINE INFUSION PRESERVES SPINAL CORD FUNCTION FOLLOWING INJURY.

Ronald F. Tuma, Temple Univ. Philadelphia, PA, USA.

16:00 - 16:15 COFFEE BREAK

16:15 - 17:30 SYMPOSIUM: CARDIAC FUNCTION

Chair: Riad N. Younes, Fac. Medicina. Univ. São Paulo, São Paulo, Brazil.

Luis F. Poli Figueiredo, Fac. Medicina. Univ. São Paulo, São Paulo, Brazil.

EFFECTS OF HYPERTONIC SALINE/DEXTRAN RESUSCITATION ON MYOCARDIAL PERFUSION AND FUNCTION IN THE PRESENCE OF A CRITICAL CORONARY STENOSIS

Martin Welte, Klinikum Grosshadern, Munich, Germany.

HYPERTONIC SALINE AND THE ISCHEMIC HEART: PRACTICAL CONCERNS.

Nguyen D. Kien, Univ. California, Davis, CA, USA.

# SALT 7

## SEVENTH INTERNATIONAL SYMPOSIUM ON HYPERTONIC RESUSCITATION

November, 14, 1996

07:30 - 12:00 REGISTRATION

08:00 - 10:00 SYMPOSIUM: RED BLOOD CELL SUBSTITUTES AND HYPERTONIC SOLUTIONS IN HYPOVOLEMIC SHOCK

Chair: George C. Kramer, Univ. Texas Medical Branch, Galveston, TX, USA.  
Reuven Rabinovici, Jefferson Medical College, Philadelphia, PA, USA.

CURRENT STATUS OF HEMOGLOBIN BASED OXYGEN CARRIES

Kenneth E. Burhop, Baxter Healthcare Corp., Round Lake, IL, USA.

SMALL VOLUME RESUSCITATION: ROLES FOR CRYSTALLOIDS, COLLOIDS AND OXYGEN CARRIERS.

George C. Kramer, Univ. Texas Medical Branch, Galveston, TX, USA.

RED BLOOD CELL SUBSTITUTES AND HYPERTONIC SOLUTIONS IN HYPOVOLEMIC SHOCK.

*Florence Pollack* Reuven Rabinovici, National Naval Medical Center, Bethesda, USA.

COMBINED INFUSION OF HYPERTONIC SALINE AND LIPOSOME ENCAPSULATED HEMOGLOBIN IMPROVES OUTCOME OF SEVERE CONTROLLED HEMORRHAGIC SHOCK.

Reuven Rabinovici, Jefferson Medical College, Philadelphia, PA, USA.

SMALL VOLUME RESUSCITATION WITH HEMOGLOBIN ALONE AND HYPERTONIC-HEMOGLOBIN SOLUTIONS

Luis F. Poli de Figueiredo, Fac. Medicina Univ. São Paulo, São Paulo, Brazil.

10:00 - 10:15 COFFEE BREAK

10:15 - 12:15 SYMPOSIUM: MECHANISMS OF HYPERTONIC RESUSCITATION

Chair: Hiromaru Ogata, Tokyo Univ. Tochigy, Japan.

Konrad Messmer, Klinikum Grosshadern, Munich, Germany

MICROCIRCULATORY ASPECTS OF HYPERTONIC RESUSCITATION

Eliete Bouskela, Univ. Estado Rio de Janeiro, Rio de Janeiro, Brazil.

HYPERTONIC SOLUTIONS AND LIVER PERFUSION

Konrad Messmer, Klinikum Grosshadern, Munich, Germany.

VASCULAR PERMEABILITY CHANGES IN EXPERIMENTAL SEPTIC SHOCK

Eric Svensjö, Univ. Estado Rio de Janeiro, Rio de Janeiro, Brazil.

SURVIVAL FOLLOWING VARIOUS REGIMENS OF FIRST TREATMENT IN SEVERELY BLEED DOGS.

M. Rocha e Silva, Research Division, Heart Institute, Fac. Med. Univ. São Paulo, São Paulo, Brazil.

EFFECT OF HYPERTONIC SOLUTIONS ON HIPPOCAMPAL CA1 AREA FOLLOWED BY ISCHEMIA AND REPERFUSION.

Hiromaru Ogata, Tokyo Univ. Tochigy, Japan.

12:15 - 14:00 POSTERS / LUNCH

14:00 - 16:00 SYMPOSIUM: CLINICAL TRIALS AND MILITARY USES

Chair: Stephen P. Bruttig, US Army Research and Materiel Command, Frederick, MD, USA.

~~Charles Wade, San Jose, CA, USA~~

HYPERTONIC SALINE DEXTRAN (HSD) FOR RESUSCITATION OF PRE-HOSPITAL TRAUMA IN THE U.S. ARMY: PAST, PRESENT, FUTURE.

Stephen P. Bruttig, US Army Research and Materiel Command, Frederick, MD, USA.

SMALL-VOLUME HYPERTONIC RESUSCITATION: GENERAL STRATEGY AND PRECLINICAL RESULTS IN CENTRAL EUROPE.

Uwe Kreimeier, Klinikum Grosshadern, Munich, Germany.

FEASIBILITY OF SMALL VOLUME FLUID RESUSCITATION ON THE BATTLEFIELD

M. Dubick, US Army Inst. Surgical Research, San Antonio, TX, USA.

~~HYPERTONIC SALINE USE IN MILITARY COMBAT~~

~~Michael Krausz, Carmel Medical Center, Haifa, Israel.~~

HSD CLINICAL TRIALS: A METANALYSIS OF INDIVIDUAL PATIENT FILES.

~~Charles Wade, San Jose, CA, USA~~

*James Holcomb* *UC, Davis*

16:00 - 16:15 COFFEE BREAK



## **SALT 7**

# **SEVENTH INTERNATIONAL SYMPOSIUM ON HYPERTONIC RESUSCITATION**

**16:15 - 17:30 SYMPOSIUM: PROSPECTS FOR FUTURE USE.**

Chair: Mauricio Rocha e Silva, Fac. Medicina Univ. São Paulo, São Paulo, Brazil.

### **CELLULAR EFFECTS**

Karl -E Arfors, Experimental Medicine, Inc., Princeton, NJ, USA.

### **SYSTEMIC EFFECTS ( CIRCULATION )**

George C. Kramer, University of Texas Medical Branch, Galveston, TX, USA.

### **CLINICAL USES**

Mauricio Rocha e Silva, Fac. Medicina Univ. São Paulo, São Paulo, Brazil.

**SALT 7**  
**7<sup>TH</sup> INTERNATIONAL CONFERENCE ON HYPERTONIC RESUSCITATION**  
**November, 13 & 14, 1996**  
**ABSTRACTS**

- S 01 The Role of Key Solutes for Small Volume Resuscitation: Hypertonic Crystalloids, Hyperoncotic Colloids & O<sub>2</sub> Carriers**  
GC Kramer, M Rocha e Silva, CE Wade, LF Poli de Figueiredo  
University of Texas Medical Branch, TX, USA
- S 02 Inhaled Nitric Oxide Reverses Pulmonary Hypertension Induced by Cell-Free Hemoglobin Preliminary Results**  
LF Poli de Figueiredo, M Mathru, D Solanki, GC Kramer  
University of Texas Medical Branch, TX, USA
- S 03 Differential Expression of Cytokine mRNA in Liver and Spleen Following Infusion of Liposome Encapsulated Hemoglobin (LEH)**  
X-L Zhu, ND Pacheco, FM Rollwagen  
Resuscitative Medicine Program, Naval Medical Research Institute, Bethesda, MD, USA
- S 04 Pancreatic Enzyme Activity Following Hypertonic Saline Dextran or Dextran or Lactated Ringer's Resuscitation of Severe Burn in Sheep**  
MA Dubick, MP Kinsky, GC Kramer  
US Army Inst Surgical Research, MTR Branch, San Antonio, TX, USA
- S 05 Effect of Repeated HSD Infusion on Heart Function in 40% TBSA Burn, A Blinded, Prospective Trial in Conscious Sheep**  
GI Elgio, LF Poli de Figueiredo, B Mathews, PJ Schenarts, GC Kramer  
University of Texas, Medical Branch, TX, USA
- S 06 Orally Administered IL-6 as Prophylaxis for Sepsis Following Hemorrhagic Shock**  
FM Rollwagen, Y-Y Li, ND Pacheco, X-L Zhu, Y-H Kang  
Resuscitative Medicine Program, Naval Medical Research Institute, Bethesda, MD, USA
- S 07 Comparison of Hypertonic Saline-Dextran and Normal Saline in Female Dogs with Septic Shock**  
DT Fantoni, JOC Auler Jr, F Futema, M Faustino, SRG Cortopassi, ER Migliatti, CM Oliveira  
Veterinary Hospital, Univ. São Paulo, São Paulo, Brazil
- S 08 Effects of Hypertonic NaCl Solution on Microvascular Hemodynamics in Normo and Hypovolemia**  
E Bouskela  
Laboratório de Pesquisas em Microcirculação, Univ. Estado Rio de Janeiro, Rio de Janeiro, Brazil
- S 09 Microvascular Permeability Increased by Endotoxin may be Inhibited by Intravenous Hypertonic Saline**  
E Svenslo, H Carvalho-Gama, JA Matos  
Laboratório de Pesquisas em Microcirculação Univ. Estado Rio de Janeiro, Rio de Janeiro, Brazil
- S 10 Effects of Hypertonic Saline, Ringer's Lactate With and Without 3% Dextran on Endotoxin Induced Changes in Plasma Volume**  
JA Matos, H Carvalho-Gama, E Svensjö, E Bouskela  
Laboratório de Pesquisas em Microcirculação, Univ. Estado Rio de Janeiro, Rio de Janeiro, Brazil
- S 11 Evaluation of Hemodynamic Effects of Etomidate Compared to Ketamine in the Anesthetic Induction of Hemorrhagic Shocked Dogs**  
ADO Fraga, GN Oide, AA Ludovico, R Prist, JOC Auler Jr, M Rocha e Silva  
Instituto do Coração, Departamento de Anestesiologia, Fac. Med. Univ. São Paulo, São Paulo, Brazil
- S 12 Hypertonic Saline Dextran Improves Liver Perfusion and Function in Rats After Hemorrhagic Shock**  
CO Corso, D Rüttinger, R Leiderer, K Messmer  
Institute for Surgical Research, University of Munich, Germany



- S 13 Effects of NaCl 7.5% in The Cat Mesenteric Microcirculation After Hemorrhage**  
H Carvalho-Gama, IP Torres Filho, E Bouskela  
Dept of Physiological Sciences, Inst. Biol., Univ. Estado Rio de Janeiro, Rio de Janeiro, Brazil
- S 14 Hypertonic Sodium Chloride ( NaCl 7.5% ) Raises the Oxygen Availability in the Tissues**  
SV Trivellato, D Birolini  
Department of Emergency Surgery, Intensive Care Unit, São Paulo University, Brazil
- S 15 Hypertonic Saline/Dextran in Normovolemic and Hypovolemic Healthy Volunteers Increase Interstitial and Intravascular Fluid Volumes**  
S Tølløfsrud, T Tønnessen, Ø Skraastad, H Noddeland  
Department of Anaesthesia, Rikshospitalet, Norway
- S 16 Hypertonic NaCl ± Dextran 70 Treatment of Acute Myocardial Infarction**  
LM Waagstein, H Haljamäe, F Waagstein, E Wennberg  
Dept Anesthesia and Intensive Care, Sahlgrenska University Hospital, Göteborg, Sweden
- S 17 Hypertonic Saline and Gastric Mucosal Microcirculation in ICU Patients**  
M Dahlqvist, H Haljamäe, E Wennberg  
Department of Anesthesiology and Intensive Care, Sahlgrenska University Hospital, Göteborg, Sweden
- S 18 Hemodynamic Effects of a Dextran-Hypertonic Saline Solutions in Sepsis**  
E Oliveira, R Weingartner, ES Oliveira, UL Sant'ana, PR Cardoso, FA Alves, RP Oliveira, G Friedman  
Intensive Care Unit, Santa Casa Hospital, Porto Alegre, Brazil
- S 19 Treatment of Hemodynamic Instability with Hypertonic Saline During Endoscopic Resection of a Pheochromocytoma**  
U Strecker, M Lipp  
Dept of Anesthesiology, University Mainz, Germany
- S 20 Hypertonic Saline in Normovolemic Volunteers**  
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Dept of Anesthesiology & Intensive Care Medicine, Graz, Austria
- S 21 Acute Hypotension in Anesthetized Patients Caused by Hypertonic Saline**  
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Dept of Anesthesiology & Intensive Care Medicine, Graz, Austria
- S 22 Cohort Analysis of Hypernatremia on Survival of Patients with Traumatic Hypotension: Efficacy of Hypertonic Saline Dextran (HSD) Resuscitation**  
CE Wade, JJ Grady, GC Kramer, RN Younes, JW Holcroft  
Medisan Pharmaceutical, Uppsala, Sweden  
Univ. of Texas Medical Branch, Galveston, TX, USA  
Univ. of São Paulo School of Medicine, São Paulo, São Paulo, Brazil  
University of California, Davis Medical Center, Sacramento, California, USA
- S 23 NaCl 7.5% Decreases Lung Neutrophil Accumulation but Induce Perivascular Edema in the Early Phase of Shock Treatment**  
ND Mori, PD Branco, SK Kubo, R Poggetti, B Fontes, R Younes, PH Saldiva, D Birolini  
Disciplina de Trauma, Hospital das Clínicas, Fac. Med. Un. São Paulo, São Paulo, Brazil
- S 24 Hypertonic Saline/Dextran Attenuates Early Activation of Leukocytes After Traumatic Brain Injury**  
R Härtl, K-E Arfors, M Ruge, J Ghajar  
Virchow-Klinikum, Medizinische Fakultät der Humboldt-Universität zu Berlin- Germany  
Cornell University Medical College, New York, USA
- S 25 The Effect of Small Volume Resuscitation on Focal Cerebral Low Flow Conditions After Venous Occlusion**  
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Inst Neurosurgical Pathophysiology, University Mainz, Germany
- S 26 US Navy's Blood Research Program: Goals, Projects and Funding Opportunities**  
CL Shake, L Yaffe  
Naval Medical R&D Command, National Naval Medical Center, Bethesda, MD, USA

- S 27 Combined Infusion of Hypertonic Saline and Liposome Encapsulated Hemoglobin Improves Outcome of Severe Controlled Hemorrhagic Shock**  
R Rabinovici, A Rudolph  
Thomas Jefferson University, Department of Surgery, Philadelphia, PA, USA
- S 28 Current Status of Hemoglobin Based Oxygen Carriers**  
KE Burhop  
Baxter Healthcare Corp. Blood Substitutes Program, Round Lake, IL, USA
- S 29 Vascular Permeability Changes in Experimental Septic Shock**  
E Svensjö  
Laboratório de Pesquisas em Microcirculação, Univ. Estado Rio de Janeiro, Rio de Janeiro, Brazil
- S 30 Survival Following Various Regimens of first Treatment of Severely Bled Dogs.**  
M Rocha e Silva R Prist, ESV França,  
Research Division, Heart Institute, Fac. Med. Univ. São Paulo, São Paulo, Brazil.
- S 31 Hypertonic Sodium Chloride Improves Delayed Neuronal Death of Hippocampal CA-1 Followed by Ischemia and Reperfusion**  
H Ogata, S Hamaguchi, S Yamaguchi, X Xluo, X Xu  
Dept Anesthesia, Univ Tochigy, Japan
- S 32 Hypertonic Saline Dextran (HSD) for Resuscitation of Prehospital Trauma in the US Army: Past, Present, Future**  
SP Bruttig  
Deputy Director, Combat Casualty Care Research Program, US Army Medical Reser  
Fort Detrick, Frederick, MD, USA
- S 33 Feasibility of Small Volume Fluid Resuscitation on the Battlefield**  
MA Dubick  
US Army Inst Surgical Research, MTR Branch, San Antonio, TX, USA
- S 34 Current Perspectives of Prehospital and Clinical Use of Small-Volume Resuscitation in Central Europe**  
U Kreimeier, K Peter, K Messmer  
Dept of Anesthesiology & Inst. für Surg. Research  
Ludwig-Maximilians-University Munich, Klinikum Grosshadern, Munich, Germany

## S-1

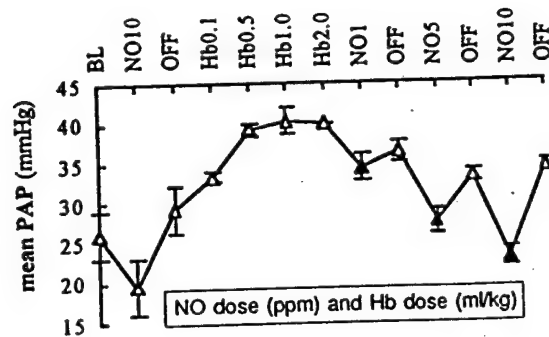
**THE ROLE OF KEY SOLUTES FOR SMALL VOLUME RESUSCITATION: HYPERTONIC CRYSTALLOIDS, HYPERONCOTIC COLLOIDS & O<sub>2</sub> CARRIERS** GC Kramer, M Rocha e Silva, CE Wade & LF Poli de Figueiredo UTMB, Galveston, TX

Several solutes have been suggested for the key components of solutions for small volume resuscitation of hypovolemic shock. Hyperosmotic crystalloid solutions, e.g. NaCl (HS), rapidly expand plasma volume, increase venous return and cardiac output. HS may also improve cardiac contractile function and redistribute cardiac output away from skin and muscle towards more vital organs. The addition of a hyperoncotic colloid such as dextran (D) slightly increases and greatly sustains the volume expansion and improved cardiovascular function. HSD is the most widely studied formulation and significantly increases discharge survival in patients with traumatic injury and hypotension when infused as the initial treatment of shock. Some of the effectiveness of HSD may involve the ability of HS to reverse cellular membrane depolarization and upregulate immune function, while the D component may inhibit white cell margination in the microcirculation and be an antioxidant. A limitation of HSD is that its volume expansion reduces the O<sub>2</sub> content of blood. Oxygen carrier solutions of either hemoglobin (Hb) or perfluorocarbon (PF) are under development. Hb alone and HS-liposome encapsulated Hb have been studied for small volume resuscitation and a hypertonic PF solution has been tested in experimental cardiopulmonary bypass. Liposome encapsulated Hb or the PF solutions produce very low oncotic pressures and should benefit from the addition of a colloid. Alternatively, Hb alone is a colloid and could be used as the hyperoncotic component of a small volume solution. Initial studies have shown potential benefit of a hyperosmotic, hyperoncotic oxygen carrier solution, but final development may await the regulatory approval of a safe and effective oxygen carrier.

## S-2

**INHALED NITRIC OXIDE REVERSES PULMONARY HYPERTENSION INDUCED BY CELL-FREE HEMOGLOBIN. PRELIMINARY RESULTS.** LF Poli de Figueiredo, M Mathru, D Solanki, GC Kramer, Dept. Anesthesiology, Univ Texas Med Branch, Galveston, USA

Severe pulmonary hypertension may offset benefits of cell-free hemoglobin blood substitutes. We hypothesized that inhaled nitric oxide (INO) selectively reverses pulmonary hypertension induced by cell-free hemoglobin. We performed experiments in fentanyl-anesthetized pigs using INO (1, 5 and 10 ppm), in 10 min intervals followed by 10 min of O<sub>2</sub> alone, in four different scenarios: a) during baseline conditions, b) after cumulative infusion of 0.05 to 2 ml/kg of a 10% solution of  $\alpha\alpha$  cross-linked hemoglobin ( $\alpha\alpha$ Hb) c) after a 4 ml/kg bolus of  $\alpha\alpha$ Hb, infused after 45 min of hemorrhagic shock (MAP=40 mmHg) and d) INO by mask, spontaneous ventilation, after 2 ml/kg  $\alpha\alpha$ Hb. INO 10 ppm caused a ~23% decrease in baseline pulmonary arterial pressure (PAP). Infusion of  $\alpha\alpha$ Hb caused a 53% increase in PAP in normovolemic and 43% in hemorrhaged pigs. INO in 1 ppm partially, and in 5 and 10 ppm completely, reversed pulmonary hypertension induced by  $\alpha\alpha$ Hb in normovolemic and hemorrhaged pigs, during mechanical or spontaneous ventilation. There were no systemic hemodynamic changes related to INO. We conclude that inhaled NO is a highly effective treatment to selectively counteract the pulmonary hypertension induced by free-hemoglobin blood substitutes.



## S-3

**DIFFERENTIAL EXPRESSION OF CYTOKINE mRNA IN LIVER AND SPLEEN FOLLOWING INFUSION OF LIPOSOME ENCAPSULATED HEMOGLOBIN (LEH).** X-L. Zhu, N.D. Pacheco and F.M. Rollwagen, Naval Medical Research Institute, Bethesda, MD USA.

LEH, a blood substitute, has been evaluated in the treatment of hemorrhagic shock as a resuscitation fluid. Immune responses following its administration remain to be determined. We showed that plasma IL-6 was significantly increased in mice after LEH transfusion without increase in plasma TNF, IL-1 or IFN- $\gamma$ . IL-6 mRNA expression in macrophage and endothelial cell lines was markedly increased by LEH administration. Cytokine mRNA expression in livers, spleens, lungs and kidneys after LEH injection was determined by semi-quantitative RT-PCR and in situ hybridization. The results showed that IL-6 mRNA accumulation in livers and spleens was enhanced at 4 h following LEH injection and declined at 24 h. mRNA for other cytokines of the inflammatory series (TNF, IL-1 and GM-CSF) were also increased, but only IL-6 was secreted *in vivo* and *in vitro*. No IL-6 mRNA was found in kidneys or lungs of treated mice. In livers, IL-6 mRNA expression was located in endothelium of blood vessels, hepatic sinuses and epithelial cells of the bile ducts. In addition, lymphocytes, hematopoietic cells and macrophages were observed expressing IL-6 mRNA in spleens. The data shows that besides the reticuloendothelial system, other cells can increase IL-6 production following administration of foreign substances.

## S-4

**PANCREATIC ENZYME ACTIVITY FOLLOWING HYPERTONIC SALINE DEXTRAN OR LACTATED RINGER'S RESUSCITATION OF SEVERE BURN IN SHEEP.** M.A. Dubick, M.P. Kinsky and G.C. Kramer, US Army Inst. Surg. Res., San Antonio, TX 78234 and Univ. Texas Med. Br., Galveston, TX 77550, USA.

Recent studies have documented that pancreatitis is a serious, frequent complication after major burn injury. The present study examined exocrine pancreatic enzyme activity and antioxidant status following burn injury and fluid resuscitation. Anesthetized sheep (n=7/gp) received a 70%

TBSA (30% full thickness) scald burn. Fluid resuscitation was begun 30 min after injury with 10 ml/kg 7.5% NaCl/6% Dextran-70 (HSD) or lactated Ringer's (LR) to maintain  $O_2$  delivery ( $DO_2$ ). Animals were euthanized 8 h after scalding and tissue collected. HSD was as effective as LR in maintaining  $DO_2$  and hemodynamic stability, but at 22% of the fluid volume required in the LR group. Scald burn and LR resuscitation resulted in significantly higher trypsin and chymotrypsin, but not amylase, specific activity (U/mg protein) compared with sham burned controls. In addition, burn injury resulted in 53% higher pancreatic malondialdehyde and 136% higher conjugated diene levels, as indices of lipid peroxidation, compared with controls. Of the antioxidant enzymes assayed, only pancreatic glutathione reductase specific activity was significantly lower in burned sheep. HSD infusion tended to lower the elevated digestive enzyme activity and indices of lipid peroxidation, but the values were still significantly higher than controls. These data suggest that severe burn injury results in oxidative stress to the pancreas with elevated levels of proteinases. HSD resuscitation of burn injury may reduce fluid requirements and edema, but further work is necessary to elucidate any benefit on burn-associated pancreatic dysfunction.

## S-5

EFFECT OF REPEATED HSD INFUSION ON HEART FUNCTION IN 40% TBSA BURN - A BLINDED, PROSPECTIVE TRIAL IN CONSCIOUS SHEEP. G.I. Elgio, L.F. Poli de Figueiredo, B. Mathews, P.J. Schenarts, G.C. Kramer. Dept. Anesth., Univ. Texas Med. Branch, Galveston, TX.

We tested the hypothesis that a repeated dose of hypertonic saline dextran (7.5% NaCl / 6% dextran 70; HSD) could prolong or reinforce the beneficial effect of a single dose. A 40% total body surface area flame burn was inflicted on preinstrumented, anesthetized sheep. 1 hr after burn and recovery from anesthesia, a 4 ml/kg dose HSD was given over 30 min (n=6). This was immediately followed by lactated Ringer (LR), adjusted to maintain urine output 1-2 ml/h the next 22½ hr. At 12 hr, a second dose HSD 4 ml/kg was given over 5 hr, concurrent with LR infusion. Controls (n=6) received normal saline. Hemodynamic data was recorded hourly, and tissue blood flows measured using colored microspheres at baseline before burn (BL), 2, 12 and 24 hr after burn. At 24 hr, animals were anesthetized and hearts removed, and right ventricular capillary muscle was tested for maximum contractility in a tissue bath. Cardiac index (CI), ventricular work indexes (LVWI, RVWI) and myocardial blood flow (MBF) decreased markedly after burn. The initial HSD dose caused rapid increase in CI, and return to BL within 12 hr. CI in controls only returned to BL at 21 hr. LVWI and RVWI transiently increased to BL with HSD, and recovered to BL within 12 hr in both groups. MBF was reduced after HSD only in the control group. Significant differences between groups were present for 3-12 hours only. This study supports previous findings that HSD infusion early after severe burn significantly improves heart mechanical function. A beneficial effect on myocardial contractility also appears to be present at 24 hr. However, the second, slowly infused dose of HSD had no detectable effect on hemodynamic parameters.

## S-6

ORALLY ADMINISTERED IL-6 AS PROPHYLAXIS FOR SEPSIS FOLLOWING HEMORRHAGIC SHOCK. F.M. Rollwagen, Y.-Y. Li, N.D. Pacheco, X.-L. Zhu and Y.-H. Kang. Naval Medical Research Institute, Bethesda, MD 20889-5607

Orally administered IL-6 has been shown to reduce bacterial translocation from the intestines of hemorrhaged mice and rats. The mechanism(s) for such beneficial effects have not been elucidated. We investigated the ability of oral IL-6 to affect microcirculation in the ileum following hemorrhage. Doppler flow measurements, as well as EM studies using iv administered HRP, showed that blood circulation was markedly reduced following hemorrhage with resuscitation. Following IL-6 administration, however, the intestinal microcirculation was again patent as demonstrated by increased HRP permeability and Doppler flow. Intraluminal HRP was shown to pass between intestinal epithelial cells of hemorrhaged mice, but not in hemorrhaged mice fed IL-6 or normal mice. Since the IL-6 effect on intestinal microcirculation occurs within 3-5 minutes, as measured by Doppler flow, it is unlikely that enzymatic digestion of IL-6, which reaches maximum in 30 minutes *in vitro*, can completely abrogate the effect. We propose that a mechanism of action of IL-6 in intestinal ischemia is to relax the intestinal microvasculature, thereby allowing restored oxygenation of tissues.

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## S-7

COMPARISON OF HYPERTONIC SALINE-DEXTRAN AND NORMAL SALINE IN FEMALE DOGS WITH SEPTIC SHOCK. D.T. Fantoni, J.O.C. Auler Jr, F. Futema, M. Faustino, S.R.G. Cortopassi, E.R. Migliatti, C.M.Oliveira. Veterinary Hospital -USP- São Paulo.

Hypertonic saline-dextran solution (HSD) have been used successfully in several experimental models of hemorrhagic shock and some emergency situations. However the clinical use of HSD during septic shock still remains controversial. The aim of this study was to compare the effects of HSD and normal saline (NS) solutions in fourteen female dogs with septic shock due to pyometra and scheduled for ovariohysterectomy. Before anesthesia, a score evaluating heart and respiratory rate, mean arterial pressure (MAP), pH, bicarbonate plasma level, capillary refill time as well as behavior were applied to established the degree of shock and were used as an inclusion criteria. All animals were submitted to the same anesthetic protocol and maintained with isoflurane in 100% oxygen and breathing spontaneously. Animals were randomly allocated to receive 4ml/kg of HSD (2400 mOsm of sodium chloride, 6 % dextran-70), or normal saline (32ml/kg). A Swan-Ganz and a femoral artery catheter were inserted for hemodynamic evaluation and blood sample collection. All parameters were measured immediately before and 5 and 20 minutes after HSD or NS administration. Survival rates were analyzed one week post-operatively. HSD caused significant increases in MAP, cardiac output and systolic indexes. Except for MAP which remained

unchanged in the NS group, the results were similar. CVP, PAP and PAWP increased significantly with NS. The comparison between the two groups showed that only the PAP values were statistically different. A substantial increase in  $\text{DO}_2$  and a decrease in  $\text{C(a-v)O}_2$  were observed with both regimens. Oxygen extraction ratio decreased significantly in the HSD group. Hemodilution occurred in both regimens, and in regard to bicarbonate plasma levels and arterial blood gases, no difference was observed between HSD or NS. One animal of the NS group died 48 hs after the surgical procedure. In conclusion, both solutions were capable to produce similar effects, however only the HSD improved MAP in shocked animals.

## S-8

EFFECTS OF HYPERTONIC NaCl SOLUTION ON MICROVASCULAR HEMODYNAMICS IN NORMO- AND HYPOVOLEMIA. E. Bouskela. Lab. de Pesquisas em Microcirculação, IB/UERJ, Rio de Janeiro, Brazil.

The aims of this study were to investigate possible resuscitation effects of a single, 10 min, 350  $\mu\text{l}$  intravenous infusion of 7.5% NaCl in hamsters in hemorrhagic shock and to compare the effects of such infusion with an identical one of 0.9% NaCl on the hamster cheek pouch microcirculation during normovolemia and after acute bleeding to a hypotension level of about 40 mmHg. No significant differences could be detected between the effects of either infusion given to normovolemic normotensive hamsters. In the animals subjected to hemorrhage, upon bleeding, arterioles larger than 40  $\mu\text{m}$  constricted, arterioles smaller than 40  $\mu\text{m}$  dilated and venular diameter did not change, while blood flow decreased in all vessels. The main differences between the infusions after hemorrhage were a significant increase in mean arterial pressure and arteriolar blood flow, venoconstriction and a tendency for the smaller arterioles to remain more dilated and the larger ones more constricted after the hypertonic infusion. Central nervous and/or reflex excitation of the sympathetic nervous system could account for the constriction of venules and larger arterioles, while a direct effect of hyperosmolality could explain the dilatation of the smaller arterioles. The study can therefore help to explain some of the mechanisms underlying the reported resuscitation effect of 7.5% NaCl infusion in animals during severe hemorrhagic hypovolemia.

## S-9

MICROVASCULAR PERMEABILITY INCREASE BY ENDOTOXIN MAY BE INHIBITED BY INTRAVENOUS HYPERTONIC SALINE. E. Svensjö, H. Carvalho-Gama, J.A. Matos. Lab. de Pesquisas em Microcirculação, IB/UERJ, Rio de Janeiro, Brazil.

Septic or endotoxin shock is characterized by profound changes in plasma volume due to increased vascular permeability. The present study was aimed to study effects of locally applied endotoxin to hamster cheek pouch microvasculature and its modulation by hypertonic saline given i.v. prior to endotoxin. The cheek pouch was studied

by intravital microscopy using FITC-labelled dextran as tracer of macromolecular permeability increase. *Escherichia coli* lipopolysaccharide (7  $\mu\text{g/ml/min}$ ) was continuously added into the superfusion buffer of the cheek pouch preparation during 180 min in one group ( $n=6$ ) without treatment and in another group ( $n=6$ ) given hypertonic saline 7.5 %, 3.5 ml/kg during 4 min, 15 min prior to the start of endotoxin application. The number of postcapillary venular leaks were recorded with 10 min intervals. Endotoxin application caused a reversible increase in the number of postcapillary venular leaks with a maximal response ( $109 \pm 3$  leaks/ $\text{cm}^2$ ) seen at 70 minutes of superfusion in the untreated control group. There was a significant difference between the number of leaks in the two groups ( $p<0.05$ ) already after 30 min application of endotoxin which was maximal following 70 min superfusion. The maximal response to endotoxin was reduced to  $50 \pm 4$  leaks/ $\text{cm}^2$  in the hypertonic saline treated group. Thus hypertonic saline 7.5% given i.v. prior to local application of endotoxin made the endothelium and/or the circulating leukocytes less susceptible to endotoxin stimulation which resulted in a reduced plasma leakage in postcapillary venules of the cheek pouch.

## S-10

EFFECTS OF HYPERTONIC SALINE, RINGER'S LACTATE WITH AND WITHOUT 3% DEXTRAN ON ENDOTOXIN INDUCED CHANGES IN PLASMA VOLUME. J.A. Matos, H. Carvalho-Gama, E. Svensjö, E. Bouskela. Lab. de Pesquisas em Microcirculação, IB/UERJ, Rio de Janeiro, Brazil.

Intravital microscopy studies of the cheek pouch of hamsters given endotoxin 0.3 mg/kg i.v. induced changes in vasomotion which could be counteracted by continuous infusions of Ringer's lactate (RL) and RL with 3% dextran (RLD) but not by hypertonic saline 7.5% (HS). Our aim was now to study changes in vascular permeability following the same dose of endotoxin and with the same fluid treatment. Plasma loss was estimated from measurements of hematocrit (Hct) and extravasation of a plasma marker, FITC-dextran, ( $\text{Mw}=150\,000$ ) into the peritoneal cavity and into the trachea. Hamsters were divided into five groups ( $n=6$ ), one untreated control and 4 groups receiving endotoxin 0.3 mg/kg followed by no further treatment (LPS), hypertonic saline 7.5%, 3.5 ml/kg, (HS), Ringer's lactate 6.5 ml/kg (RL) and Ringer's lactate with 3% dextran (RLD), 6.5 ml/kg. FITC-dextran concentrations were measured in plasma and in postmortem lavage fluids of the peritoneal cavity and of the trachea. Hct increased ( $p<0.05$ ) in the LPS [ $51.6 \pm 2.5 \rightarrow 59.7 \pm 6.2\%$ ] and HS [ $53.5 \pm 3.0 \rightarrow 58.8 \pm 5.0\%$ ] groups, was unchanged in the RL and reduced ( $p<0.05$ ) in the RLD group. FITC-dextran concentrations in tracheal lavage fluid were similar in all groups but increased ( $p<0.05$ ) in the peritoneal lavage fluid of HS, RL and RLD groups as compared with the untreated control and LPS groups. Thus endotoxin induced reductions in plasma volume could be counteracted by continuous fluid treatment as seen with RL and RLD but not with hypertonic saline treatment. Endotoxin induced plasma leakage into the peritoneal cavity was not counteracted by any treatment.



## S-11

EVALUATION OF HEMODYNAMIC EFFECTS OF ETOMIDATE COMPARED TO KETAMINE IN THE ANESTHETIC INDUCTION OF HEMORRHAGIC SHOCKED DOGS. A.D.O. Fraga, G.N. Oide, A.A. Ludovico, R. Prist, J.O.C. Auler Jr., M. Rocha e Silva. Exp. Anest. Dept. Incor HC-FMUSP, Brazil.

Hemorrhagic shock causes severe hemodynamic compromise and represents a challenge mainly in clinical situations when the patient needs to be anesthetized. The aim of this study was to compare the hemodynamic effects of two agents employed in anesthesia induction of animals submitted to an experimental model of severe hemorrhagic shock. Thirty-two adult, healthy, male mongrel dogs, weighing 15 to 20 Kg, were randomly divided in four groups: GI-ketamine/normal saline; GII-ketamine/ hypertonic sodium chloride (7.5%); GIII-etomidate/normal saline; GIV-etomidate/ hypertonic sodium chloride. One day before the experimental procedure, the animals were sedated and a Swan Ganz catheter was inserted. The following parameters were evaluated: heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), cardiac index (CI), systemic and pulmonary vascular resistance indexes (SVRI, PVRI). Data was collected according to the following protocol: t0- control; t1- animals were bled to shock (mean 510  $\pm$  35 ml of blood loss in 30 min.) according to a model proposed by Rocha e Silva (1992); t2 - animals were ascribed to receive infusion of NaCl 0.9% (32ml/kg) or NaCl 7.5% (4ml/kg) in five minute period; t3- intravenous injection of etomidate (1mg/kg) or ketamine (4mg/kg) and tracheal intubation; t4- end of the protocol (15 minutes after anesthesia induction). The data were analyzed by means of analysis of variance (ANOVA  $p < 0.05$ ). Except in GIV, in which MAP remained stable, a significant decrease in this parameter in the other groups was observed. In G1, cardiac index fell slightly, and remained stable in the other groups. HR, PVRI, SVRI and CVP increased significantly with ketamine, and remained stable in the etomidate groups. In conclusion, ketamine or etomidate are safe for anesthetic induction in shocked animals resuscitated either with saline or hypertonic solutions, however the etomidate group showed better hemodynamic performance with no harmful side effects.

## S-12

HYPERTONIC SALINE DEXTRAN IMPROVES LIVER PERFUSION AND FUNCTION IN RATS AFTER HEMORRHAGIC SHOCK. C.O. Corso, D. Rüttinger, R. Leiderer and K. Messmer. Institute for Surgical Research, University of Munich, Munich, Germany.

Hemorrhagic shock induces severe liver injury due to sinusoidal perfusion failure. Reduced perfusion pressure and endothelial swelling, along with activation of Kupffer cells and leukocytes enhance nutritive perfusion failure and compromise liver function. Small Volume Resuscitation is known to restore the microvascular flow. Male Wistar Dextran-resistant rats were anesthetized, mechanically ventilated, bled and maintained at MAP 40 mmHg for 1h. The animals were resuscitated with NaCl 7.2%/10% Dextran 60 (HSD, 10% shed volume/2min, n=8); 6% Dextran 60 (DEX, 100% shed volume/5min, n=8) or Ringer Lactate (RL, 4-fold shed volume/20min, n=6). By intravital microscopy at baseline, at 1h shock, and after 1h resuscitation sinusoidal perfusion was analysed, bile was collected and arterial ketone body ratio (AKBR) determined. Shock induced a significant increase in the number of nonperfused sinusoids in all groups (~30%). After 1h resuscitation the sinusoidal perfusion was significantly improved in HSD ( $17.8 \pm 0.8\%$  nonperfused

sinusoids) compared with DEX ( $21.8 \pm 0.7\%$ ,  $P < 0.05$ ) and RL ( $23.9 \pm 0.9\%$ ,  $P < 0.01$ ). Bile flow amounted to ~2.8  $\mu\text{l/min/g}$  of liver at baseline and was severely reduced at 1h shock ( $P < 0.05$  vs baseline). After 1h resuscitation HSD improved bile flow ( $P < 0.05$  vs 1h shock) whereas RL and DEX had no positive effect. At 1h shock AKBR was only  $0.16 \pm 0.03$ . A significant improvement was achieved only with HSD treatment ( $0.42 \pm 0.05$ ,  $P < 0.01$ ). Both RL ( $0.23 \pm 0.04$ ) and DEX ( $0.28 \pm 0.03$ ) were not able to ameliorate the redox potential of the liver. HSD proved superior in restoring microvascular liver perfusion, and therefore, improving liver energy status and function.

## S-13

EFFECTS OF NaCl 7.5% IN THE CAT MESENTERIC MICROCIRCULATION AFTER HEMORRHAGE.

H. Carvalho-Gama, I.P. Torres Filho, E. Bouskela. Dept. of Physiological Sciences, IB/UERJ, Rio de Janeiro, Brazil.

In this study we investigated the effects of NaCl 7.5% on mean arterial pressure (MAP) and on mean internal diameter of mesenteric arterioles (range 12.6 to 67.4  $\mu\text{m}$ ) and venules (range 11.7 to 74.9  $\mu\text{m}$ ) in 17 cats of either sex, mean weight 2.4 kg. MAP was reduced to 60 mmHg by hemorrhage (volume withdrawn  $17 \pm 5$  ml/kg). Anesthesia was induced by ketamin and maintained with  $\alpha$ -chloralose (38 mg/kg). The femoral artery and vein were cannulated for pressure measurements, the carotid artery and the jugular vein for hemorrhage and infusion, respectively. The microcirculation was observed using an intravital microscope coupled to a closed circuit TV system. The TV monitor display was used to measure internal diameter of the studied vessels during the control period, after hemorrhage and after the infusion of NaCl 7.5%, 4 ml/kg in 10 min. MAP was  $123 \pm 3$  mmHg before and 60 mmHg, after hemorrhage and  $72 \pm 2$  mmHg following NaCl 7.5% infusion. After hemorrhage, arterioles and venules  $>45$   $\mu\text{m}$  constricted (47 and 36%, respectively) while the arterioles  $<45$   $\mu\text{m}$  did not change and the venules dilated. After NaCl 7.5%, arterioles and venules  $>45$   $\mu\text{m}$  dilated (23 and 45%, respectively) while the smaller arterioles and venules constricted (30 and 49%, respectively). Our results show beneficial effects with the use of NaCl 7.5 % after hemorrhage at the microcirculatory level of the cat mesentery.

## S-14

HYPERTONIC SODIUM CHLORIDE (NaCl 7.5%) RAISES THE OXYGEN AVAILABILITY IN THE TISSUES.

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Shoemaker [1988] stated in his publication, that the treatment of the high risk patients is based in increasing the oxygen supplies. Considering that the maintenance of the oxygenation parameters in levels

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above the normal decreases the morbidity and increases survival in high risk surgical patients, twenty high risk patients in non hemorrhagic shock were studied possible hemodynamic and oxygenation effects of a NaCl 7.5% solution (hypertonic sodium chloride) infusion.

Among the findings, we outlined:

1. The infusion of NaCl 7.5% solution in a dose of 5 ml/kg raises the oxygen availability in the tissues.
2. The improvement of hemodynamic parameters was notorious after infusion of a NaCl 7.5% solution in a dose of 5 ml/kg of the solution in patients with non hemorrhagic shock.

### S-15

**HYPERTONIC SALINE/DEXTRAN IN NORMOVOL-EMIC AND HYPOVOL-EMIC HEALTHY VOLUNTEERS INCREASE INTERSTITIAL AND INTRAVASCULAR FLUID VOLUMES.**  
S. Tølløfsrud, T. Tønnessen, Ø. Skraastad, H. Noddeland. Dept. Anaesth. Rikshospitalet, Oslo, Norway.

The effects of i.v. hypertonic saline 75 mg·ml<sup>-1</sup> in dextran 70, 60mg·ml<sup>-1</sup> (HSD) infusion on fluid shifts between the interstitial and intravascular fluid spaces, diuresis and hemodynamics were studied in healthy volunteers. Nine fasting subjects received 4ml·kg<sup>-1</sup> HSD as a 10 min infusion in a normovolemic situation. Seven days later they served as their own controls in a hypovolemic situation after 10% of the calculated blood volume was withdrawn during a 15 min period. Before and after the HSD infusion, interstitial colloid osmotic pressure (COP) and interstitial fluid hydrostatic pressure (P<sub>i</sub>) were measured. HSD infusion caused a transitory unpleasant sensation of headache and heat in the thorax up to the throat and a transitory haemodynamic effect with increased heart rate (HR), increased mean arterial pressure (MAP) from 77±5 mmHg to 92±13 mmHg (p<0.05) and central venous pressure (CVP) from 5±1 mmHg to 8±1 mmHg (p<0.05) after end of infusion. A haemodilution with an increase in calculated blood volume lasting longer than the MAP was observed, with decreased COP<sub>i</sub> from 14.4±2.2 mmHg to 12.1±2.0 mmHg (p<0.05). A more pronounced effect was observed during moderate hypovolemia. Conclusions: HSD infusion resulted in hemodilution and increase in calculated blood volume with increased HR, MAP, and CVP. These effects were more pronounced in a hypovolemic situation. The hemodilution was caused by fluid shift from the intracellular compartment hydrating the interstitial and vascular fluid spaces and increasing the diuresis.

### S-16

**HYPERTONIC NaCl ± DEXTRAN 70 TREATMENT OF ACUTE MYOCARDIAL INFARCTION.**

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Negative as well as positive inotropic cardiac effects of hypertonic saline (HS) have been previously reported. The aim of the present study was to investigate the hemodynamic and myocardial effects of normal saline (NS), 7.5% HS, and 7.5% HS-Dextran-70 (HSD) treatment following experimental acute myocardial ischemia.

Acute myocardial ischemia was induced (clip on LAD) in anesthetized pigs (n=34) during 45 min. Prior (5 min) to the release of the clip an infusion (4 mL/kg) of NS, HS, or HSD was started (total infusion period - 10 min) and central hemodynamics (HR, MAP, CI, SVR, LV+dp/dt, LVEDP, MPAP, PVR, PCWP, CVP), blood chemistry, and cardiac cell damage (ASAT, CK-MB, CK, Troponin-T, high energy phosphagen levels) were monitored. The heart was at 240 min perfused (Evans blue and triphenyltetrazolium chloride), sliced and the areas of normal, at risk, and infarcted myocardium were quantified.

The hemodynamics did not differ between the groups during the LAD occlusion and the markers of cardiac cell ischemia remained unchanged with the exception of Troponin-T which increased about 0.03 µg/L. At reperfusion serum levels of Na and osmolality increased in HS and HSD groups (p<0.0001). CI increased, and SVR and PVR were reduced initially in the HS and HSD groups. The serum levels of the myocardial ischemic markers were elevated in all groups, ASAT more in the HSD than in the NS and HS groups. No significant differences in myocardial infarction or at risk areas could be demonstrated between the groups.

It is concluded that treatment of acute myocardial ischemia with HS/HSD results in beneficial hemodynamic effects. No significant reduction of the myocardial ischemic damage by HS/HSD could be demonstrated.

### S-17

**HYPERTONIC SALINE AND GASTRIC MUCOSAL MICROCIRCULATION IN ICU PATIENTS.**

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Previous reports have demonstrated positive effects of hypertonic saline (HS) on the microcirculation in different organ systems. Measurements of mucosal pH have indicated that the gastrointestinal microcirculation is commonly disturbed in critically ill patients. The aim of the present study was to investigate the effects of HS on central hemodynamics and gastric mucosal blood flow in ICU-patients.

Critically ill patients (n=15) requiring ventilatory and hemodynamic support and demonstrating laboratory evidence of hepatic or renal dysfunction were included in the study which was approved by the local Ethics Committee. Infusion of HS (7.5% NaCl) 4 ml/kg b.w. was given to all patients (infusion period 20 min). Central hemodynamics and blood chemistry were intermittently monitored from 90 min before infusion until 2 h after start of infusion. Blood flow in gastric mucosa was continuously monitored by laser-doppler flowmetry (Perimed AB, Sweden) using a specially designed probe. Gastric tonometric catheters were used for simultaneous measurements of intramucosal pH (pHi).

Infusion of HS was associated with an immediate increase in CI and decrease of SVR and PVR. The gastric mucosal blood flow response was more sluggish but an increase of 30 - 250% was observed 30 to 45 min after the start of the infusion of HS. Then the mucosal blood

flow decreased but was still above baseline at the end of the 2 h study period.

It is concluded that treatment with HS of ICU patients results in transient beneficial effects on central hemodynamics and gastric mucosal blood flow.

## S-18

### HEMODYNAMIC EFFECTS OF A DEXTRAN-HYPERTONIC SALINE SOLUTION IN SEPSIS.

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**Objectives:** We evaluated with a double-blind-placebo controlled study the effects in myocardial function of a dextran-7.5% hypertonic saline solution (HSS) in patients with sepsis.

**Material and Methods:** 25 patients with sepsis (CONSENSUS SCCM-1992), with PAOP <12 mmHg, hemodynamically stable. The patients were randomized to receive 250 ml of saline (GI, n=15) or SSH (GII, n=10). Hemodynamic and metabolic variables were measured before and then 30, 60, 120 180 min after the start of a 10 min bolus. The groups were comparable at admission study for all demographic and clinical variables and APACHE II.

#### Results:

TIME	CI l/min.m <sup>2</sup>	SI ml/bat.m <sup>2</sup>	PAOP mmHg	NA mEq/l
0 min GI	4.34±1.53	39.74±13.0	5.47±2.77	139±7
GII	4.33±1.25	40.15±14.5	6.90±2.33	140±7
30min GI	4.52±1.53#	41.30±12.8	6.87±3.07#	137±7#
GII	6.06±1.79*	52.96±15.9	10.67±3.04*	146±2
60 min GI	4.18±1.46#	41.93±15.9	7.33±3.06#	—
GII	5.57±1.66	48.59±10.9	10.20±2.82*	—
120 min GI	4.32±1.48#	41.74±13.0	8.27±3.67*	—
GII	5.82±1.75*	56.07±24.3*	9.30±1.70*	—
180min GI	4.20±1.08	42.37±12.8	9.20±4.09*	136±8#
GII	4.88±1.61	48.35±20.9	9.00±2.50	143±5

#p<0.05 GI vs GII. \*p<0.05 vs time 0. CI: cardiac index, SI: sistolic index, PAOP: pulmonary artery occlusion pressure, Na: sodium

**Conclusion:** The dextran-hypertonic saline solution is safe. The HSS was more efficient than placebo in the volume resuscitation of stable septic patients.

## S-19

### TREATMENT OF HEMODYNAMIC INSTABILITY WITH HYPERTONIC SALINE DURING ENDOSCOPIC RESECTION OF A PHEOCHROMOCYTOMA. U. Strecker, M. Lipp.

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Release of catecholamines, acute lack of intravascular volume and pressure transmitted to intrathoracic organs cause difficulties in the volume therapy during retroperitoneal endoscopic resection of a pheochromocytoma. A high risk patient (coronary disease, cardiomyopathy, chronic bronchitis) was anesthetized with isoflurane and fentanyl. Hypertonia was treated with dibenzylran and sodium nitroprusside. Dilatation of the retroperitoneum and manipulation of the tumor caused hemodynamic instability. Systolic blood pressure drifted between 100 and 190 mmHg. Heart rate rose to 110 b.s<sup>-1</sup>, accompanied with signs of coronary ischemia (ECG-lead V<sub>5</sub>: -0.3 mV). Heart insufficiency as well as the increase of total peripheral resistance (TPR) up to 3050 Dyn\*s\*m<sup>2</sup>/cm<sup>5</sup>, combined with a reduced preload (compression of the v. cava inf.) resulted in a marked critical decrease of the

cardiac index (from 4 to 2.4 l/min/m<sup>2</sup>). In this situation 250 ml hypertonic saline (7.5%) was infused over 5 min. Under therapy, oxygen uptake recovered rapidly from 138 to 294 ml O<sub>2</sub>/min, followed by an increase of the cardiac index to 4l/min/m<sup>2</sup> within 20 min. TPR decreased from 2800 to 2250 Dyn\*s\*m<sup>2</sup>/cm<sup>5</sup>. Previously stopped urine production rose to 200 ml/h. Systolic blood pressure, heart rate, pressure in the pulmonary artery and pulmonary capillary wedge pressure (PCWP) remained nearly unchanged. After resection of the tumor the expected hemodynamic collapse remained absent. All hemodynamic values returned to normal values, especially TPR (to 1450 Dyn\*s\*m<sup>2</sup>/cm<sup>5</sup>). This case report illustrates hypertonic saline as a successful instrument in the volume therapy during the resection of a pheochromocytoma.

## S-20

### HYPERTONIC SALINE IN NORMOVOLEMIC VOLUNTEERS. W. Kröll, S. Izmail, S. Sabutsch, S.E. Gaßmayr, W. Pöltz, W. Schimetta, W.F. List. Dept. of Anesthesiology & Intensive Care Medicine, Graz, Austria.

**Objective:** The intravenous infusion of hypertonic saline-hydroxyethylstarch (HS-H) causes rapid mobilization of endogenous fluids, which results in an adequate restoration of hemodynamics. In an experimental study infusion of HS-H in normovolemic animals exerts only minimal effects on circulatory variables; therefore the aim of the present investigation was to evaluate what happens after infusion of HS-H in normovolemic volunteers. **Method:** 4mL/kg bw of the following solutions have been infused within 7.5 minutes to 4 healthy volunteers: Ringer's lactated solution, 10% HES 100/0.5, 10% HES 200/0.5, 7.2% NaCl-10% HES 200/0.5 (HS-H). Volume changes were calculated from the measurements of plasma and blood density and hematocrit; changes of plasma and blood density were measured using the mechanical oscillator method (MOT). **Results:** Infusion of HS-H resulted in an increase of plasma volume of about 420 ml immediately at the end of infusion. This effect lasted for about 30 minutes and then decreased to about 290 ml after 1 hour and to 130 ml after 2 hr. after the end of the infusion. After infusion of 10% HES 200/0.5 an inward shift of about 280 ml was seen. This effect also lasted for 30 minutes and then decreased. The increase in plasma volume after 10% HES 100/0.5 was 400 ml. This effect however was only of short duration: 30 minutes after the end of infusion the increase in plasma volume was about 110 ml and 90 minutes after the end of infusion the effect was over. The infusion of lactated Ringer's solution results only in an outward shift of fluid. **Conclusion:** The infusion of HS-H in normovolemic volunteers results, compared to the application of this solution in hypovolemic patients, in a small and short-lasting increase in plasma volume. The infusion of HS-H in normovolemic volunteers results, compared to the application of this solution in hypovolemic patients, in a small and short-lasting increase in plasma volume.

## S-21

### ACUTE HYPOTENSION IN ANESTHETIZED PATIENTS CAUSED BY HYPERTONIC SALINE. S. Izmail, W. Kröll, S.E. Gaßmayr, S. Sabutsch, W. Pöltz, W. Schimetta, W.F. List. Dept. of Anesthesiology & Intensive Care Medicine, Graz, Austria.

**Objective:** Rapid infusion of hypertonic saline (HS) causes acute hypotension in anesthetized dogs. This effect is secondary to a decrease of systemic vascular resistance. The aim of the present investigation was to verify whether



this effect can also be seen in patients or in healthy volunteers under different conditions. **Method:** Part 1: 4mL/kg bw of the following solutions have been infused within 5 minutes to 18 anesthetized patients: 10% HES 200/0.5 and 7.2% NaCl-10% HES 200/0.5 (HS-H). Part 2: 4mL/kg bw of the following solutions have been infused within 5 minutes to 12 healthy volunteers: Ringer's lactated solution, 10% HES 100/0.5, 10% HES 200/0.5 and 7.2% NaCl-10% HES 200/0.5 (HS-H). Blood pressure measurements have been done every minute during infusion and in 15 minute-intervals after infusion up to 1 hr after the end of infusion. **Results:** Part 1: In anesthetized patients MAP decreases in the HS-group from an initial value of  $76 \pm 15.5$  mmHg to  $49.3 \pm 12.6$  mmHg at the end of infusion and returns to initial value 5 min after the end of infusion ( $76 \pm 14.6$  mmHg) and then remains stable during the observation period. In the HES-group no significant changes in MAP during the study period were seen. Part 2: No significant changes of blood pressure could be observed during the observation period between the tested volume expanders in volunteers. **Conclusion:** Rapid infusion of HS causes acute hypotension in anesthetized, normovolemic patients, an effect which could not be observed in awake volunteers. An explanation for this effect could be that counteracting endocrine reactions are blocked during anesthesia in contrast to awake humans. Our results lead to the conclusion that HS should be given with caution intraoperatively in patients, in whom acute hypotension may be deleterious.

## S-22

**COHORT ANALYSIS OF HYPERNATREMIA ON SURVIVAL OF PATIENTS WITH TRAUMATIC HYPOTENSION: EFFICACY OF HYPERTONIC SALINE DEXTRAN (HSD) RESUSCITATION.** C.E. Wade, J.J. Grady, G.C. Kramer, R.N. Younes and J.W. Holcroft. Medisan Pharmaceutical, Uppsala Sweden; Univ. of Texas Medical Branch, Galveston, TX, USA; Univ. of Sao Paulo School of Medicine, Sao Paulo, Brazil; Univ. of California, Davis Medical Center, Sacramento, CA, USA.

The effect of prior dehydration on survival of patients with hypotension due to trauma is not well defined. In animal models the presence of dehydration prior to hemorrhage greatly reduces survival and the ability to resuscitate. We conducted a cohort analysis of 1060 patients receiving standard of care (SOC) or HSD to assess the effect of the presence of hypernatremia on survival. Hypernatremia was selected as being indicative of prior dehydration. Patients with the highest serum sodium levels (10%) upon admission were identified in both treatment groups. These patients were compared to the rest of the population. In hypernatremic (HYPER) patients survival until discharge was significantly decreased,  $\Delta = 41\%$ , compared to eunatremic (EU) patients. Survival was also reduced compared to survival predicted by TRISS. Patients with hypernatremia treated with HSD (HYPER+HSD) had an increase in survival compared to HYPER, even when adjusted for differences in predicted survival.

	EU	HYPER	HYPER+HSD
N	487	51	54
Na <sup>+</sup> (mEq/l)	$141 \pm 4$	$150 \pm 4$ *	$162 \pm 11$ ◊
RTS	$5.5 \pm 2.2$	$4.5 \pm 2.5$ *	$5.0 \pm 2.2$
TRISS X 100 (%)	$73 \pm 38$	$50 \pm 43$ *	$66 \pm 38$ ◊
Survival (%)	80.9	39.2 *	68.5 ◊

\* EU vs. Hyper  $p < 0.05$ ; ◊ Hyper vs. Hyper+HSD

The presence of hypernatremia (dehydration) greatly reduces survival until discharge, and if these patients are treated with HSD there appears to be a benefit.

## S-23

**NaCl 7.5% DECREASES LUNG NEUTROPHIL ACCUMULATION BUT INDUCE PERIVASCULAR EDEMA IN THE EARLY PHASE OF SHOCK TREATMENT.** N.D.Mori, P.D.Branco, S.K.Kubo, R.S.Poggetti, B.Fontes, R.N.Younes, P.H.Saldiva, D.Birolini. Department of Surgery - University of São Paulo School of Medicine.

Early infusion of isotonic saline solution is the standard treatment for hemorrhagic shock (HS) in trauma patients. Recent investigations have suggested the use of 7.5% NaCl solution as a practical and effective alternative to isotonic saline in the treatment of HS. Polymorphonuclear neutrophil (PMN) activation, sequestration and release of toxic products have been implicated in the pathogenesis of organ injury, SARA and MOF following HS. Our purpose was determine the effect of NaCl 7.5% on lung neutrophil sequestration and pulmonary edema in animals resuscitated from HS. Wistar male germ-free rats (weight  $241.85 \pm 46.06$ g) were subjected to subclavian vein (SCV) and carotid artery (CA) cannulation, and randomized into 4 groups: SHAM (N=16); SHOCK (N=15) 15 min bleeding via SCV till the mean arterial pressure (MAP) stabilized at 45-50 mmHg, followed by 60 min of shock; SF (N=13) shock for 60 min and treated with NaCl 0.9% at 4 mL/kg and observed for 20 more min; HYPER (N=15) same as SF but, treated with NaCl 7.5% at 4 mL/kg. Mean arterial pressure (MAP) was continuously recorded. Lung PMN sequestration was assessed by lung MPO determination, and lung morphometry by \*point and counting method. Data are presented as Mean $\pm$ SD and statistical analyses performed using one way analyses of variance to MAP and Kruskal-Wallis for the others variables. \*  $p < 0.05$  vs SHAM; ◊ =  $p < 0.05$  vs SHOCK; ◊ =  $p < 0.05$  vs SF.

GROUP	MAP (mmHg)	LUNG MPO (U/g tissue)	No. Points
SHAM	$102.5 \pm 25.55$	$0.98 \pm 0.44$	$2.58 \pm 1.33$
SHOCK	$44.87 \pm 6.03$	$1.58 \pm 0.61$ *	$5.03 \pm 1.96$ *
SF	$62.54 \pm 9.34$ ◊	$1.55 \pm 0.54$ *	$4.13 \pm 2.08$ ◊
HYPER	$84.67 \pm 10.71$ ◊	$1.30 \pm 0.47$ ◊	$6.95 \pm 4.08$ ◊

In conclusion, hypertonic solution is more effective in MAP restoration and induces less lung PMN sequestration, but provokes higher perivascular edema in the lung than isotonic saline.

## S-24

**HYPERTONIC SALINE/DEXTRAN ATTENUATES EARLY ACTIVATION OF LEUKOCYTES AFTER TRAUMATIC BRAIN INJURY**

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Traumatic brain injury (TBI) leads to early recruitment of inflammatory cells (WBCs) from the cerebral microcirculation. Hypertonic saline/Dextran (HS/DEX) yields promising results in the treatment of TBI. We wanted to test the hypothesis that HS/DEX modulates the acute inflammatory response to TBI.

**Methods:** Nineteen anesthetized rabbits equipped with chronic cranial windows underwent lateral fluid-percussion injury (3.5 atm). Intravital fluorescence videomicroscopy allowed quantification of pia vessel diameters, venular shear rates and WBC/endothelium interaction over 7 h in 3 experimental groups. Group I: Sham (n=5); Group II: Trauma & 4mL/kg 7.5% NaCl/10% Dextran 60 at 10 min after TBI (n=7); Group III: Trauma & 4mL/kg normal saline (n=7).

**Results:** HS/DEX significantly attenuated the number of

firmly adherent WBCs/mm<sup>2</sup> vessel wall at 6 h after TBI (35±6 vs. 200±23 in the normal saline group, baseline 22±6 and 19±3, respectively). Intracranial pressure increased after TBI and was not affected by HS/DEX. Post-traumatic increase of arterial diameters, however, was prevented by HS/DEX.

**Conclusion:** Based on the present findings the question whether the anti-inflammatory effect of HS/DEX plays a role in reducing secondary brain damage or systemic complications of TBI should be investigated further.

## S-25

### THE EFFECT OF SMALL VOLUME RESUSCITATION ON FOCAL CEREBRAL LOW FLOW CONDITIONS AFTER VENOUS OCCLUSION.

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Brain trauma or cerebral ischemia are accompanied by regional low-flow which may secondarily aggravate the primary insult. After selective occlusion of two adjacent cortical veins a large low-flow territory develops in rats, which turns into a venous infarct of variable size. This model was used to evaluate the efficacy of small volume resuscitation (SVR). Veins were occluded by photochemical activation of rose bengal via local fiberoptic illumination. 30 min after venous occlusion infusions were initiated: (1) 7.5% NaCl + 10% HES 200,000/0.5, 4ml/kg, n=9; (2) HES 10% 200,000/0.5, 4ml/kg, n=8 (3) 0.9% NaCl, 4ml/kg, n=10. rCBF was measured for 2h at 36 locations in a scanning procedure using a computer controlled micromanipulator with the occluded veins central to the scanning field. After 2 d infarct sizes were determined histologically. There was a 60-75% decrease of rCBF after vein occlusion in all groups, typical for the low-flow zone developing. In group 1 SVR induced an immediate 102% improvement of flow as compared to group 3 and a 45% improvement compared to group 2. After 2h observation flow improvements were still 112% and 40%, respectively. Accordingly the infarct sizes (largest cross sectional area) were significantly reduced by SVR: 1.5±0.1mm<sup>2</sup> vs. 3.2±0.5mm<sup>2</sup> (group 2) and 4.6±0.6mm<sup>2</sup> (group 3). The data indicate that SVR may be of benefit in conditions that are accompanied by low-flow conditions such as head injury or cerebral ischemia.

## S-26

**US NAVY'S BLOOD RESEARCH PROGRAM: GOALS, PROJECTS AND FUNDING OPPORTUNITIES.** CL Shake, L Yaffe - Naval Medical R&D Command - Bureau of Medicine and Surgery - Department of the Navy - Bethesda - MD - USA.

The United States Navy has a critical need to place a light weight, long-acting physiologic, oxygen-carrying substitute far forward on the battlefield and aboard combatant ships to serve as a resuscitative aid. Recognizing the natural and physiologic

potential of hemoglobin, Navy researchers have examined various hemoglobin delivery formulations to meet the Navy's requirement. To that end, liposome encapsulation of the hemoglobin within a lipid bilayer has been the primary approach followed by Navy investigations. Initial studies have demonstrated that liposome encapsulated hemoglobin (LEH) alleviates many of the toxicities associated with stroma-free hemoglobin administration. Investigators are diligently working on demonstrating safety and efficacy in non-human primates prior to initiating clinical trials. The results of these initiatives as well as the Navy's plans, approach, funding, and expectations for future blood product and related resuscitation studies will be presented.

## S-27

**COMBINED INFUSION OF HYPERTONIC SALINE AND LIPOSOME ENCAPSULATED HEMOGLOBIN IMPROVES OUTCOME OF SEVERE CONTROLLED HEMORRHAGIC SHOCK.** R. Rabinovici, A. Rudolph. Dept. Surg. Jefferson Med. College, Phila., and Naval Res. Lab., Washington, D.C.

The concept of hypertonic saline (HTS) treatment of trauma patients with hemorrhagic shock was developed to sustain hemodynamic stability with low-volume fluid administration. While this treatment modality has been shown to rapidly expand the intravascular volume it has no oxygen-carrying capacity and therefore does not improve oxygen delivery directly. Consequently, the addition of oxygen-carrying capability to HTS solutions appears to be one logical step to improve tissue oxygenation during acute resuscitation. To test this notion, lyophilized liposome encapsulated hemoglobin (LEH), an experimental oxygen-carrying fluid, was reconstituted with HTS and tested for its efficacy to improve outcome in controlled hemorrhagic shock. Hypotension was induced in rats by withdrawal of 70% of blood volume (1 ml/min) and therapy (n=10-16) with HTS (5 ml/kg), LEH (5 ml/kg), lactated ringer's solution (v:v = 1:3), LEH-HTS (5 ml/kg) or oxygen (100%) was initiated 15 min later. LEH-HTS improved skeletal muscle oxygen tension (PO<sub>2</sub> 87 ± 13 mmHg vs. 40-50 mmHg in other groups, P<0.05), hypotension, acidosis, and survival at 24 hr (75% vs. 6-25% in other groups, P<0.05). These results demonstrate for the first time a remarkable salutary effect of HTS-LEH infusion in the treatment of hemorrhagic shock. Furthermore, it provided direct evidence that this combination therapy improves peripheral tissue oxygen tension, the ultimate goal in the treatment of post-traumatic hypotension.

## S-28

**CURRENT STATUS OF HEMOGLOBIN BASED OXYGEN CARRIERS.** Kenneth E. Burhop. Baxter Healthcare Corp., Blood Substitutes Program, Round Lake, IL 60073 USA

Several companies are pursuing different research strategies to develop, manufacture

and market an effective alternative to blood transfusion for the treatment of trauma and blood loss in surgery patients. Such oxygen-carrying solutions also have potential in the treatment of critical disease conditions arising from inadequate oxygen delivery or tissue perfusion, such as stroke, sepsis, and heart attack. At the current time, numerous companies are in various stages of clinical trials, ranging from early phase 1 trials, to phase III pivotal efficacy trials, in each of these indications. The current status of these clinical trials, the clinical indications being pursued, as well as the various manufacturing approaches that are being investigated, will be discussed. In addition, some of the current controversies in the field that under a great deal of basic research, such as the pharmacologic properties of hemoglobin, relevant preclinical animal models, "second generation product" strategies, etc., will also be discussed.

### S-29

**VASCULAR PERMEABILITY CHANGES IN EXPERIMENTAL SEPTIC SHOCK** E. Svensjö, Lab. de Pesquisas em Microcirculação, Rio de Janeiro, Brazil.

Septic shock with multiorgan failure due to severe gram-negative bacterial infections continues to be a major problem despite effective antibiotics and supportive care. The core glycolipid portion of endotoxin or lipopolysaccharide (LPS) is believed to play an important role in the pathophysiology and pathogenesis of gram-negative sepsis and shock. The vascular endothelium is a critical target for endotoxin and many cytokines released during gram-negative sepsis. More specifically it appears from several studies as if the endothelium of postcapillary venules is the important target for LPS or cytokines. Thus local application of endotoxin to the hamster cheek pouch microvasculature caused extravasation of plasma (FITC-dextran) from postcapillary venules and also an increased sticking of leukocytes in the same venules. In an experimental septic shock model in rats the most effective therapy in terms of survival and conservation of plasma volume was a combination of i.v. fluid, glucocorticoid and  $\beta_2$ -receptor agonist supporting the hypothesis that counteraction of endothelial cell contraction by glucocorticoid and  $\beta_2$ -agonist could reduce plasma loss. In another rat model based on endotoxin infusion there was a clear inhibition of hematocrit increase by a  $\beta_2$ -agonist. Endotoxin given i.v. to sheep induced marked increases in plasma extravasation in liver and lungs which was counteracted by a  $\beta_2$ -agonist. It is not suggested that  $\beta_2$ -agonists should be included in therapies for fluid loss prevention but this type of studies suggest that means to neutralize the action of endotoxin and related cytokines on postcapillary venular endothelium are of therapeutic interest.

### S-30

**SURVIVAL FOLLOWING VARIOUS REGIMENS OF FIRST TREATMENT OF SEVERELY BLED DOGS.**

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**Objective.** To determine the effects of various treatment regimens and their sequence in the survival of severely hemorrhaged dogs. **Method:** Seventy four male mongrel dogs ( $17.2 \pm 0.2$  kg) were bled to a mean arterial pressure (MAP) 35-40 mm Hg in 15 min. and held at that MAP for 30 min. (bled volume:  $48.2 \pm 0.8$  mL/kg), when bleeding was interrupted and treatment started. Five min. before treatment, dogs were randomized into four groups: HSD (n=12); treated with 4 mL/kg HSD; LR (n=12); treated with 10 mL/kg LR; HSD-LR (n=25), treated by the combination, in that sequence; LR-HSD (n=25) treated in the inverted sequence. Interval between treatments in the 2 latter groups was 30 min. Dogs were monitored hemodynamically for 3 hr, then observed for 72 hr, in the kennel. Overall mortality was 75% in single treatments, 38% in double treatments; Amongst non survivors, time to death was longer in HSD vs. LR groups, and in the HSD-LR sequence, compared to the LR-HSD sequence. MAP, cardiac index, systemic vascular resistance  $DO_2$ ,  $VO_2$  were significantly improved in the HSD vs. LR treatments, as well as in the HSD-LR sequence with respect to the LR-HSD sequence, but only between treatments. **Conclusion:** HSD, as the only, or as treatment first treatment improves survival time in controlled hemorrhage, as compared, respectively to LR as the only, or as the first treatment.

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### S-31

**HYPERTONIC SODIUM CHLORIDE IMPROVES DELAYED NEURONAL DEATH OF HYPOCAMPAL CA1 FOLLOWED BY ISCHEMIA AND REPERFUSION.** H. Ogata, S. Hamaguchi, S. Yamaguchi, X. Xluo, X. Xu. 1<sup>st</sup> Dept. of Anesthesia, Tokyo Univ. Tochigi, Japan.

The present experiment was conducted to ascertain whether a small amount of HSS was effective against delayed neuronal death on the hippocampal CA1 area of the Mongolian gerbils. Twenty eight gerbils were divided into 4 groups and anesthetized with 1% halothane and 50% nitrous oxide. Their common carotid arteries were occluded bilaterally for 2.5 min immediately after which 2mL/kg of 10% NaCl was infused via the tail vein. Same volume of physiological saline solution (PSS) was injected for the control group in the same manner. Five days later, the cerebrum was removed, and the hippocampus was stained with hematoxylin-eosin. Degeneration of pyramidal cells and radial striated zone in the CA1 area were observed under the microscope. The degeneration rate of the pyramidal cells were as follows; after sham ( $4.2 \pm 1.8\%$ ), after sham operation with HSS ( $6.5 \pm 3.3\%$ ), on ischemia-reperfusion with PSS ( $95.6 \pm 1.6\%$ ), on ischemia-reperfusion with HSS ( $7.1 \pm 3.0\%$ ). Pathological change of degeneration was atrophy, nuclear pycnosis, deepstaining of the cytoplasm vacuolation, and cell structural disruption of the radial striated zone. We considered for the reason that  $Na^+$  gradient could be



properly maintained after HSS administration so as to inhibit extracellular calcium ion influx. Therefore, we made a quantitative analysis of superoxide anion in the hippocampus to determine the relationships between superoxide anion and pyramidal pathological changes. Production of superoxide anion after ischemia and reperfusion was as follows. Immediately after release:  $3.8 \pm 1.1$ ; at 6h:  $4.2 \pm 0.7$ ; at 12h:  $5.2 \pm 1.2$ ; at 1 day:  $5.0 \pm 1.8$ ; at 3 days:  $16.1 \pm 3.4$ ; at 5 days:  $10.5 \pm 1.8$ ; at 7 days:  $5.6 \pm 2$ . Superoxide anion production was increased since the 3<sup>rd</sup> day after ischemia-reperfusion with significant differences coinciding with pathological changes in the hippocampal area. These findings suggest that improvement of hippocampal area by HSS might be due suppression of superoxide anion generation.

## S-32

**HYPERTONIC SALINE DEXTRAN (HSD) FOR RESUSCITATION OF PRE-HOSPITAL TRAUMA IN THE U.S. ARMY: PAST, PRESENT, FUTURE.** S.P. Bruttig, Combat Casualty Care Research Program, U.S. Army Medical Research and Materiel Command, Ft. Detrick, Frederick, MD, USA 21702-5012

The history of combat teaches us that most combat deaths result from moderate hemorrhage due to truncal trauma or from head injury, occur forward of medical facilities, and occur within 20 minutes of wounding. To significantly reduce battlefield mortality, one must rapidly locate, diagnose and effectively treat these casualties. Army research interests, international scientific expertise, and staunch corporate support launched a comprehensive program to develop an easily administered, small volume resuscitation solution (HSD). While early studies demonstrated effectiveness of HSD in fatal controlled hemorrhage experimental models, later studies questioned the prudence of rapidly restoring vascular volume and arterial pressure in uncontrolled truncal hemorrhage. However, several clinical trials of HSD failed to demonstrate a population of trauma victims at risk from vigorous resuscitation. While the civilian clinical community has reasonable familiarity with HSD, the military community, which supported the initial research, has little or no familiarity with this solution. Thus, there is concern in the military communities that HSD may place penetrating trauma and burn casualties unnecessarily at risk. These communities must be reassured through experience that HSD is a viable option for effective, rapid fluid volume resuscitation of hemorrhagic hypotension. Research must identify the most effective, least threatening resuscitation strategies. In addition, identification of efficacious therapeutic adjuncts to HSD therapy will characterize "life after HSD". Finally, the technology explosion supporting development of non-invasive physiologic sensors will provide some quality control to early, aggressive fluid resuscitation. Such challenges represent the future, not only for HSD, but also for those products and procedures which support HSD use in pre-hospital trauma.

## S-33

**FEASIBILITY OF SMALL VOLUME FLUID RESUSCITATION ON THE BATTLEFIELD.** M.A. Dubick, U.S. Army Inst. Surg. Res., San Antonio, TX 78234, USA.

Hemorrhage from penetrating trauma remains the primary cause of death on the battlefield in conventional warfare. An

analysis of wartime casualty statistics revealed that to significantly improve combat casualty care, an improvement in field medical care, with emphasis on management of hemorrhage, must be realized. Although early, adequate fluid resuscitation is deemed essential to reduce mortality and morbidity associated with hemorrhage, logistical constraints preclude the availability of large volumes of fluid on the battlefield. In addition, under austere battlefield conditions, a major limitation of field resuscitation may be significant time delays and failures in performing venous catheterization. The advantage of hypertonic saline dextran (HSD) rapidly expanding plasma volume and stabilizing hemodynamic variables in numerous animal models of hemorrhage, at 1/10 to 1/12 the volume of conventional crystalloids, has been recognized by the U.S. Army, making HSD a potentially useful field resuscitation fluid. In recent years, the administration of HSD through an intraosseous infusion device or the application of 'limited or hypotensive resuscitation' has been explored. The results of this research suggest that many of the difficulties and concerns associated with fluid resuscitation for penetrating trauma in the field can be overcome. For the military, this has important consequences for developing improved fluid resuscitation strategies under austere battlefield conditions.

## S-34

**CURRENT PERSPECTIVES OF PREHOSPITAL AND CLINICAL USE OF SMALL-VOLUME RESUSCITATION IN CENTRAL EUROPE.** U. Kreimeier<sup>1,2</sup>, K. Peter<sup>1</sup>, K. Messmer<sup>2</sup>, Dept. of Anesthesiology<sup>1</sup> & Inst. f. Surg. Research<sup>2</sup>, Ludwig-Maximilians-University Munich, Klinikum Grosshadern, Munich, Germany.

Small-volume resuscitation (SVR) by means of hypertonic saline colloid solution has been advocated for resuscitation from severe hypovolemia and shock almost a decade ago. In Central Europe ATLS of trauma patients covers early fluid resuscitation and early intubation and ventilatory support. In this setting SVR may provide increased blood flow and thus increased  $DO_2$  to peripheral tissues. Prehospital studies, however, have not yet yielded conclusive results regarding the efficacy of SVR in terms of reduced mortality when compared to SOC. As a result of the lack in parameters available for monitoring of the microcirculation in the prehospital setting, this issue couldn't be addressed satisfactorily. However, data from clinical trials in Austria, Germany, France and Switzerland have demonstrated the volume sparing effect when SVR is used for volume substitution in cardiac bypass and in aortic aneurysm surgery, as well as in terms of augmentation of  $VO_2$  in septic patients. Current study protocols focus on the titrated use of SVR in selected groups of patients in the perioperative setting. Furthermore, head trauma patients with increased ICP refractory to conventional therapy have been treated successfully with hypertonic saline colloid solution. Among the European countries Austria is the only where hypertonic saline hydroxyethyl starch (Osmohes<sup>®</sup>) has been registered for clinical use so far. In contrast, in the trauma setting differences towards the United States exist regarding etiology (incidence of blunt trauma > penetrating trauma), strategy of ATLS, and short prehospital period. Thus establishment of indications and contraindications for small-volume hypertonic saline resuscitation await further prehospital trials and advanced logistic design with reference to defined (sub-)population of trauma patients.